Remarks

Applicant has carefully considered the Examiner's remarks bridging pages 2-4 of the Official Action, and that refer to the art references already of record. Although the Applicant agrees to amend certain claims to further separate the present invention from the prior art, Applicant must point out that, as already filed, the current claims already recite "a manipulative difference" as the Examiner has defined it, in order to already provide for this distinction.

Applicant's independent claim is already free of the prior art

The requested "manipulative difference" is already present in Claim 26 (repeated directly below) -- as it was pending immediately prior to the present amendments. The pertinent distinction is that the compound must bind under physiological conditions and be useful in the treatment of cancer.

> Claim 26 (prior form) A method for identifying organic non-peptide compounds useful in the treatment of cancer comprising the steps of contacting a mutant or wild-type mammalian protein of the p53 family, with an organic non-peptide compound, and determining whether said compound is capable of binding to one or more domains of said protein under physiological conditions and restoring or stabilizing a functional conformation therein.

Without acting as a limitation on the term "physiological conditions" as it is, in its totality, recited and used in the Specification, and also making reference also to how the present Specification is understood by those skilled in the art, the term "physiological conditions" relates, for example, to what happens, or can be made applicable to, or predictive of, events **in the body** of an patient. The *Welsch* reference is replete with numerous examples where solvents soak a sample of cells [but which is not a body] at concentrations that would be lethal to a patient. In fact, there is not a single experiment in the *Welsh* reference that would be anything other than toxic (and in almost all cases lethal) to any patient subjected to any "treatment" that is, or could be extrapolated from, the *Welsh* experiments, given the concentrations of the test substances that are needed and contemplated (for example, see Examples 2C and 4 using 1 Molar glycerol, a concentration that is physiologically lethal and certainly not drug-worthy. **Thus, there is not a single suggestion anywhere in the *Welsh* reference that any compound exists at all that would ever be effective enough to work at a dose low enough to be safe in a patient, and more**

importantly, there is no motivation offered or suggested to go looking for one. Therefore, it is obvious that the *Welsh* reference does not refer to physiological conditions, and p53 is merely mentioned therein as one of hundreds of proteins that could be bulk-stabilized under non-physiological conditions, to further *in vitro* experiments. Accordingly, *Welsh* is neither a section 102 nor a section 103 reference against the present invention.

Pages 4-5 of the Summary of the Invention Section of the present Application make more than clear that the technology disclosed in the present Specification is for the treatment of patients, to identify substances that can be safely administered to patients. (for example, see Page 5, at lines 9-11 in the Specification). Therefore, it is also not understood why the current Official Action (at page 3 thereof) contains quotes from Applicant's prior responses, since the quoted passages are precisely on point and correct, and clearly distinguish the *Welsh* reference.

Turning to the remainder of the art-related arguments in the Official Action, the Examiner states (at page 3. last paragraph) that the phrase "useful in the treatment of cancer" is a use limitation. Applicant respectfully disagrees. Beyond the fact that Applicant's claims are directed to screening, not making, the **manipulative difference is to test whether** the compound is, for example, potent enough that it could be used at doses low to qualify as a pharmaceutical, and not as a benchtop *cell pickling agent.* There is not the slightest suggestion of this inventive step in the *Welsh* reference.

Applicant has further amended the independent claim to distinguish the prior art

It should be noted that the fundamental difference between what is being looked at in the prior art, compared to the present Specification (i.e, for the first time, identifying molecules that work well enough to be effective as drugs), is outlined clearly in the present Specification itself, as would also readily be understood by those skilled in the art. Not surprisingly, the compounds successfully identified according to the methods of the present invention interact with p53-type proteins in specific fashions, not via crude "bulk effects" as disclosed in the prior art. Referring to the present Specification at Pages 15-16:

" The term **specific** interaction in this application is used to exclude unspecific forms of binding including the type known to occur between hydrophobic compounds and proteins through nonselective hydrophobic interactions. The term **specific** interaction is further used to distinguish the properties of the compounds of this invention from compounds that affect proteins thermostability by changing the chemical properties of the bulk solvent. Such molecules excluded from the scope of this aspect of the invention include thermostabilizing agents such as glycerol, trimethylamine-oxide, and deuterated water. Compounds that **specifically** interact with a protein of the p53 family will show an effect at much lower

concentrations than such bulk solvents or non-specific hydrophobic interactions. For example, glycerol is effective at 600 mM. However, effects of compounds that **specifically** interact with a protein of the p53 family will be observed at concentrations of the compound lower than 1mM, preferably lower than 100 micromolar, and more preferably lower than 10 micromolar in invitro or cell based assays." **(emphasis added)**

Accordingly, there is unambiguously a difference between Applicant's invention, as disclosed and claimed, and anything remotely taught in the cited art such as *Welsh*. Applicant has further amended Claim 26 via the present submission to further clarify these distinctions. Claim 26 has been amended to make clear that an assay in being performed, in fact, that multiple compounds are being screened. The screening method of the invention is also clearly directed not to compounds that have bulk solvent effects, for example, but rather to compounds that are capable of stabilizing the protein at concentrations which permit use as drugs, such as below 1mM. There is no example of any compound in *Welsh* that functions *specifically*, and the Welsh reference does not say that this is so, nor is it suggested that there is any motivation to look for such compounds. Should the Examiner maintain an argument that *Welsh* itself did not make, then Applicant respectfully presumes that such assertion is based on special knowledge of the Examiner, which the Applicant cannot traverse until it is made of record.

Support for the amendments to Claim 26 are further found in the Specification, for example, as follows. As aforementioned, that the invention is directed to specific interactions is explained on Page 15 of the Specification. That the DBD (DNA binding domain) of p53-type proteins is preferably targeted is also explained at Page 15. Throughout the Specification, and particularly at Page 34, it is particularly mentioned that mutant human p53 proteins, having missense mutations, and being associated very commonly with cancers, are a particularly preferred group of targets for screening to identify specifically stabilizing organic non-peptide compounds. Support for the amendments to Claim 32 are found, for example, at Page 34. Support for screening of a plurality of organic non-peptide compounds against samples of p53 family proteins, in a screening assay, is provided in the Specification, for example, from Page 33, line 27 to Page 34, line 4; Page 35, line 16 through Page 37, line 9; and in particular, through the use of microtiter plates that contemplate numerous identical protein well samples. Various methods of assaying conformation of proteins of the p53 family are described on Pages 37-38, and the assay of libraries (n the form of a plurality of compounds) is further supported at page 39, beginning at line 6, and the "re-screening" of positive compounds, i.e, the further development of leads based on positive hits is also

supported on Pages 39-40. Additional assays adaptable to high throughput mode for the screening of plurality of compounds for their ability to stabilize a functional p53 comformation are provided, for example, at Page 40, example 1, and via the methods of Example 2, using antibody methodology in cell based assays.

Antecedent basis for the term "measurement" in Claim 27 has been accomplished by amendment of Claim 26.

Conclusion

A Petition for Extension of Time (3 months) is enclosed. It is believed that the Application is in condition for allowance, and the Examiner is welcome to contact the undersigned to propose any further needed amendments to the claims. An early and favorable reply is respectfully requested.

Respectfully submitted,

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